CLINICAL MICROBIOLOGY REVIEWS, Apr. 1989, p. S18–S23
0893-8512/89/0S0S18-06$02.00/0

Vol. 2, Suppl.

Plasmids of *Neisseria gonorrhoeae* and Other *Neisseria* Species

MARILYN C. ROBERTS

Department of Pathobiology, University of Washington, Seattle, Washington 98195

All plasmids in bacteria are units which replicate independently of the bacterial chromosome, are generally less than 1/20 the size of the bacterial chromosome, and contain the information for self-replication. The 2.6-megadalton (MDa) cryptic gonococcal plasmids were first identified in the genus *Neisseria* in 1972 (13). Since cryptic plasmids had no measurable phenotype, they attracted little attention. The importance of plasmids in *Neisseria* spp. changed with the identification of β-lactamase plasmids in *N. gonorrhoeae* in 1976 (12). These plasmids encoded a β-lactamase which rendered the strains resistant to penicillin, the drug of choice for the therapy of gonorrhea at that time. As a result, β-lactamase plasmids had a great influence on the antibiotic treatment of gonorrhea. Since then, the indigenous 24.5-MDa conjugative gonococcal plasmids have been described and were shown to code for their own conjugal transfer, as well as mobilize the small gonococcal β-lactamase plasmids to other *N. gonorrhoeae* strains and *Neisseria* species (10, 16, 17, 21, 27, 32, 33). More recently, plasmids containing resistance determinants for tetracycline, sulfonamide, and other antibiotics have been described for various *Neisseria* species (14, 23–25, 28, 29, 37, 38).

Antibiotic resistance plasmids found in the genus *Neisseria* appear to be created either by direct acquisition of plasmids from other gram-negative bacteria or by the transposition of antibiotic resistance genes into indigenous neisserial plasmids. The β-lactamase and RSF1010-like plasmids are examples of direct acquisition of plasmids from other species (14, 38), whereas the 25.2 MDa TetM-containing plasmid is an example of a composite plasmid (28).

The presence of genetically related β-lactamase plasmids in both *N. gonorrhoeae* and *Haemophilus* spp. strongly suggested that plasmid exchange between these two genera had occurred in nature (4–6). Similarly, the presence of the RSF1010-like plasmids in *Neisseria* spp. indicated that plasmid exchange also occurred between the genus *Neisseria* and enteric bacteria (14, 37, 38). The 25.2-MDa plasmid has been transferred from *N. gonorrhoeae*, where it appears to have been created (28), into clinical strains of *N. meningitidis*, *Eikenella corrodens*, and *Kingella denitrificans* (22, 24, 35). Experimental studies have confirmed that the 25.2-MDa plasmid can be transferred to these species by conjugation under laboratory conditions.

In this review, I will describe the different types of plasmids currently found in the genus *Neisseria* and will indicate whether related plasmids are found in other genera as well. A summary of the plasmids discussed in this review is given in Table 1. Finding genetically related plasmids in both *Neisseria* spp. and other genera has helped to define the origin of many of the neisserial plasmids and has illustrated that the plasmids found in *Neisseria* spp. are directly related to the plasmid load carried by other bacteria which inhabit humans. On the basis of studies of the plasmids in *Neisseria* spp.; one may conclude that gene and plasmid exchange is an ongoing process in nature and predict that the number of different plasmids and associated antibiotic resistance genes will increase in the genus over time.

NEISSERIA PLASMIDS

Cryptic Plasmids

The cryptic 2.6-MDa plasmids from *N. gonorrhoeae* were first described in 1972 (13). In an initial survey, we found that 96% of clinical isolates of *N. gonorrhoeae* carried this plasmid (34). However, more recently, it has been determined that all isolates of the proline-, citrulline-, and uracil-requiring auxotype are plasmid free (8). The reason for this is unclear; however, other auxotypes can also be plasmid free, although these are rare.

The 2.6-MDa cryptic plasmid is not correlated with the virulence of the gonococcal strains, pilus production, or the pilin protein, nor is it associated with the gonococcal outer membrane proteins PI, PII, or PIII, the immunoglobulin A1 proteases, the 37-kDa iron-regulated protein, or the receptor protein for the iron-retrieving siderophores (1, 2, 19). Thus, to date, this plasmid has no known function, even though the complete nucleotide sequence has been determined (26). Korch et al. (26) proposed a model for the genetic organization of the plasmid that predicted two transcriptional units, each composed of five compactly spaced genes. The promoter of one of the transcriptional units was shown to function in *Escherichia coli*. The products of three of the five genes in this operon were identified in minicell systems. Two genes in the other transcriptional unit were expressed in minicells when transcribed from an *E. coli* promoter.

It has been suggested that large segments of the 2.6-MDa plasmid can be integrated into the gonococcal chromosome in both plasmid-bearing and plasmid-free strains (19). In a few strains the entire 2.6-MDa plasmid may be integrated into the chromosome. A deletable region that contains repeated sequences has been identified in the plasmid. It is hypothesized that these repeats are involved in site-specific recombination with the chromosome and may explain why approximately 20% of the clinical isolates examined by Hagblom et al. carried a deleted variant of the cryptic plasmid (19).

Other *Neisseria* spp. also carry cryptic plasmids (11, 22, 30, 42). In one study, 69% of the plasmid-containing *N. meningitidis* strains, 33% of the plasmid-containing *N. lactamica* strains, 9% of the plasmid-containing *N. mucosa* strains, and 14% of the plasmid-containing *N. cinerea* strains were shown to carry plasmids of various sizes that hybridize with probes made from the 2.6-MDa plasmids (22). A few cryptic plasmids which do not share deoxyribonucleic acid (DNA) sequences with the 2.6-MDa plasmid have also been identified in strains of *N. meningitidis* (30, 42) and other commensal *Neisseria* spp. (10, 16). The cryptic plasmids, found in other *Neisseria* spp., do not occur as frequently as the 2.6-MDa gonococcal plasmid, and in general they have not been as well characterized as the 2.6-MDa gonococcal plasmid (11).

Gonococcal β-Lactamase Plasmids

The β-lactamase plasmids were first isolated in 1976 and were associated with strains from Africa and the Far East

TABLE 1. Plasmid classes found in the genus *Neisseria*

Plasmid class	Species	Reference(s)
Cryptic (2.6 MDa)	*N. gonorrhoeae*	13, 19, 26, 34
	N. cinerea[a]	22
	N. lactamica[a]	22
	N. meningitidis[a]	22
	N. mucosa[a]	22
β-Lactamase[b] (2.9, 3.05, 3.2, and 4.4 MDa)	*N. gonorrhoeae*	4–13, 33, 39, 41, 43
24.5-MDa conjugative	*N. gonorrhoeae*	11, 16, 17, 32–34
25.2-MDa conjugative[c]	*N. gonorrhoeae*	23, 25, 28
	N. meningitidis	24
RSF1010-like[d] (4.9, 7.0, 8.5, and 9.4 kb)	*N. meningitidis*	14, 38
	N. mucosa	29
	N. subflava	29
	N. sicca	29
Other (29 MDa)	*N. sicca*	Robledano et al., abstract

[a] These species were shown to carry plasmids of various sizes which hybridized with probes made from the 2.6-MDa plasmid.
[b] Related plasmids are found in the genus *Haemophilus* (4).
[c] Identical plasmids are found in clinical isolates of *K. denitrificans* and *Eikenella corrodens* (24).
[d] Related plasmids are found in enteric bacteria and *Eikenella corrodens* (37).

(12, 31). However, these plasmids are now endemic in isolates from North America, the Caribbean, and Europe, as well as Africa and Asia. They carry a TEM β-lactamase which hydrolyzes the cyclic amide bond in the β-lactam molecule and inactivates benzylpenicillin, ampicillin, and cephaloridine substrates but has low activity against isoazolyl penicillins such as oxacillin and methicillin (20). Originally, two plasmids were recognized at 4.4 and 3.2 MDa; each carried the TEM β-lactamase gene and 40% of Tn*A* transposon, which is the most frequent β-lactamase-encoding transposon in enteric bacteria (12, 20, 31). Recently, 2.9- and 3.05-MDa β-lactamase plasmids have been described; these appear to have been created by independent deletions of the 4.4-MDa plasmid (Fig. 1) (41, 43). The 2.9- and 3.05-MDa plasmids are not as common as the 4.4- or the 3.2-MDa plasmid.

The gonococcal β-lactamase plasmids are genetically related to small β-lactamase plasmids in various *Haemophilus* spp. (4–6, 31). These small β-lactamase plasmids from both genera are highly related and appear to represent a family of plasmids; they differ from each other by small deletions or insertions in either the Tn*A* region, which encodes the TEM β-lactamase, or the non-Tn*A* region (Fig. 1). The data indicate that these plasmids evolved from a single ancestral plasmid (4, 6, 7, 31). The small β-lactamase plasmids commonly found in *Haemophilus ducreyi* and *N. gonorrhoeae* contain 40 to 100% of the Tn*A* transposon sequences. These plasmids are less common in both *H. influenzae* and *H. parainfluenzae* (4–6, 31). The β-lactamase gene, which contains less than 100% of the Tn*A* transposon, is not transposable but gives rise to a functional transposon when linked to the left 2.4-kilobase (kb) *Bam*HI fragment from a complete Tn*A* transposon (15). These reconstructed transposons behaved like complete Tn*A* transposons because of their transposition frequencies. This suggested that the partial transposons contained the inverted repeats on the right side (IR-R) of the flanking sequence and must contain an intact fragment or a transposase (*tnpR*)-like gene. This supports the hypothesis that all the TEM β-lactamase genes originated from an intact Tn*A*-like transposon. DNA sequence analysis of the various plasmids has confirmed this hypothesis and is illustrated in Fig. 1 (5).

Gonococcal β-lactamase plasmids may be mobilized experimentally to *E. coli* or *Haemophilus* spp. by a variety of conjugative plasmids, including those from *E. coli*, *N. gonorrhoeae*, or *H. ducreyi* (4, 10, 16, 18, 27, 32, 33). However, initial attempts to transfer these β-lactamase plasmids into other *Neisseria* spp. met with only limited success (17). When introduced into the commensal *Neisseria* spp., the β-lactamase plasmids were very unstable and were quickly lost from most of the recipient strains. In a later study, Ikeda et al. (21) used the indigenous 24.5-MDa plasmid to transfer the 4.4-MDa β-lactamase plasmids from *N. gonorrhoeae* to strains of *N. meningitidis*.

Recently, using strains containing both the β-lactamase plasmid and the 25.2-MDa tetracycline resistance conjugative plasmid, we mobilized the 4.4- and 3.2-MDa β-lactamase plasmids into a variety of *Neisseria* spp., including *N. meningitidis* (36). A number of the transconjugants maintained the β-lactamase plasmids in the absence of selective antibiotic pressure. In all cases, the β-lactamase plasmid was associated with the 25.2-MDa plasmids in the transconjugants. We found that the *N. cinerea* transconjugants were exceptions to this generalization because when they were used as recipients, the β-lactamase plasmids were found without the 25.2-MDa plasmids (36). Recently, β-lactamase-producing *N. meningitidis* strains have been described (3, 9). In one case, the strain was isolated from a mixed culture with *N. gonorrhoeae* (9), and in the second case, it was not clear whether the β-lactamase enzyme was located on a plasmid or in the chromosome (3).

The small TEM β-lactamase plasmids have been transferred into *N. gonorrhoeae* and *E. coli* by transformation (31, 39). Sox et al. (39) showed that 25% of the plasmids in the gonococcal transformants had deletions, the most common of which was a 3.2-MDa plasmid. It is possible that the various gonococcal β-lactamase plasmids were created by deletions following transformation (39).

The DNA sequences of the gonococcal 4.4- and 3.2-MDa β-lactamase plasmids and the *H. ducreyi* 5.7- and 7.0-MDa β-lactamase plasmids have been determined (5). On the basis of these data and those of Yeung et al. (43) and Van Embden et al. (41), a model has been devised to account for the evolution of the small TEM β-lactamase plasmids (Fig. 1). The sequence of events hypothesized for this model is shown by the numbers 1 to 9 in Fig. 1 and explained in detail in the legend. Dickgiesser et al. (6) have suggested that the 1.8-kb insertion found in the 4.4- and 7.0-MDa plasmids, but not in the 5.7- or 3.4-MDa plasmids, is bounded by a short (200-base-pairs) terminal inverted repeat sequence and may be a bona fide insertion element.

GONOCOCCAL CONJUGATIVE PLASMIDS

24.5-MDa Conjugative Plasmids

The 24.5-MDa conjugative plasmid was first described in 1974 (11). It has been found in clinical strains of non-penicillinase-producing *N. gonorrhoeae* as well as in penicillinase-producing *N. gonorrhoeae* (11, 34), but not in any other clinical species. The prevalence of this plasmid varies geographically and temporally (34). In a recent survey of five geographical locations within the United States, the number of strains carrying the 24.5-MDa plasmid varied from 10 to

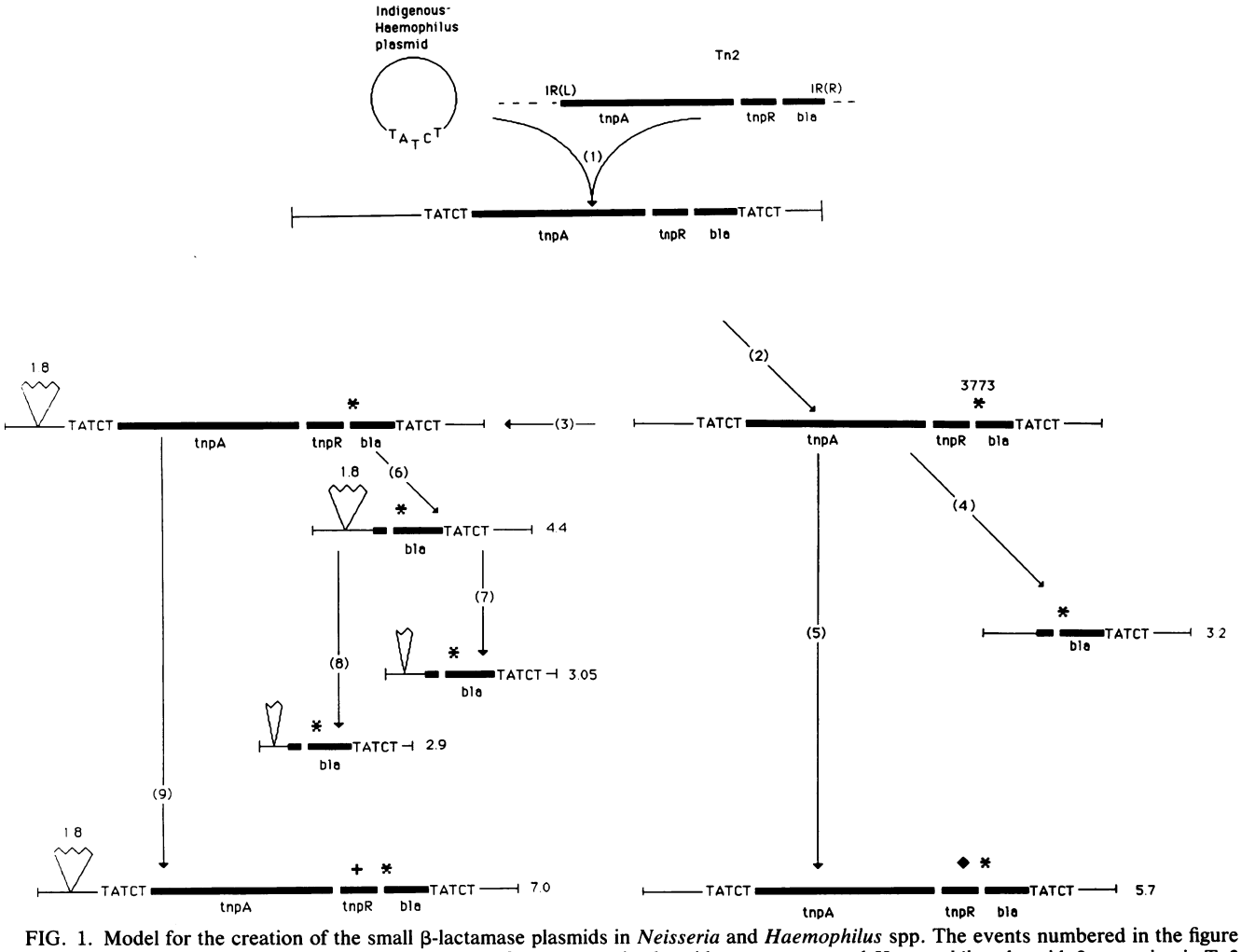

FIG. 1. Model for the creation of the small β-lactamase plasmids in *Neisseria* and *Haemophilus* spp. The events numbered in the figure are as follows. 1: Transposition of a Tn*2*-like transposon from an enteric plasmid onto an ancestral *Haemophilus* plasmid; 2: mutation in Tn*2* to replace a cytosine with a thymidine at base pair 3773 from the IR-L terminus of Tn*2* (*); 3: insertion of a 1.8-kb insertion sequence distal to IR-L; 4: deletion in the plasmid created in step 2 to produce the 3.2-MDa *N. gonorrhoeae* plasmid; 5: mutation from cytosine to thymidine (♦) in the noninsert plasmid made in step 2, to form the 5.7-MDa *H. ducreyi* plasmid; 6: independent deletion from the plasmid created in step 3, to produce the 4.4-MDa *N. gonorrhoeae* plasmid; 7: deletion of most of the 1.8-kb insert and a portion of the flanking sequences to create the 3.05-MDa *N. gonorrhoeae* "Toronto" plasmid; 8: another, separate, deletion in the same region of the plasmid to create the 2.9-MDa *N. gonorrhoeae* "Rio" plasmid; 9: mutation from guanosine to adenosine at position 3771 3′ (+) of the IR-L terminus to the form the 7.0-MDa *H. ducreyi* plasmid. The 4.4-, 3.05-, 2.9-, and 3.2-MDa plasmids have been isolated from strains of *N. gonorrhoeae*, whereas the 7.0- and 5.7-MDa plasmid have been isolated from strains of *H. ducreyi*. The other plasmids have not been isolated and are hypothetical. Data are summarized from references 5, 6, and 43.

53% (J. S. Knapp, J. M. Zenilman, R. Rice, M. C. Roberts, S. McIntire, and S. A. Morse, Sex. Transm. Dis., in press). In some cases, the 24.5-MDa plasmid is the only plasmid species present; however, it can coexist with the 2.6-MDa and the gonococcal β-lactamase plasmids (34).

The 24.5-MDa plasmid carries no detectable markers for antibiotic resistance, heavy metal, or ultraviolet resistance. However, it efficiently mobilizes itself and the smaller β-lactamase plasmids between strains of *N. gonorrhoeae* (10, 32, 33). When short mating times are used, only the β-lactamase plasmids are transferred to the recipient, whereas after overnight matings, many of the *N. gonorrhoeae* transconjugants carry both the β-lactamase and 24.5-MDa plasmids and can transfer both plasmids to other *N. gonorrhoeae* strains (32). The 24.5-MDa plasmid can also be used to mobilize the β-lactamase plasmids to other *Neiserria* spp. and *E. coli* (17, 21); however, it is not transferred to these other species. Its host range is very limited even under laboratory conditions, and other than *N. gonorrhoeae*, only certain strains of *N. cinerea* maintain it (17).

The structures of a limited number of 24.5-MDa plasmids have been determined; all had similar restriction patterns and shared 69 to 100% of their DNA sequences with two reference 24.5-MDa plasmids (34).

25.2-MDa TetM Conjugative Plasmids

The 25.2-MDa plasmid was first identified in a strain of *N. gonorrhoeae* isolated in 1982 (25). By 1985, a number of clinical isolates in North America and Europe carried this plasmid (23, 35, 28; M. C. Roberts, J. H. T. Wagenvoort, B. van Klingeren, and J. S. Knapp, Letter, Antimicrob. Agents Chemother. **32**:158, 1988). At present, the 25.2-MDa plasmid appears to be endemic in North America and has been found

in Great Britain and The Netherlands. Most of the strains in The Netherlands and a few from North America carry the 3.2-MDa β-lactamase plasmid in addition to the 25.5- and 2.6-MDa plasmids (25; Roberts et al., letter). Recently, the 24.5-MDa conjugative gonococcal plasmids have been shown to share >60% of their DNA sequences with the 25.2-MDa plasmids (28). These data have led to the hypothesis that the 25.2-MDa plasmid was formed by the transposition of the TetM determinant, encoding tetracycline resistance, onto the 24.5-MDa plasmid. The 25.2-MDa plasmids have characteristics which differ from those of the 24.5-MDa ancestral plasmids, but they have maintained the ability to move themselves and the β-lactamase plasmids to recipient strains (36). The 25.2-MDa plasmid has been associated only with the 3.2-MDa plasmid; therefore, it can be hypothesized that the 25.2-MDa plasmid was created in an *N. gonorrhoeae* population which carries the 3.2-MDa plasmid, such as in North America, Europe, Africa, or the Caribbean.

Naturally occurring strains of *N. meningitidis*, *K. denitrificans*, and *Eikenella corrodens* that carry the 25.2-MDa plasmid have been identified in both North America and Great Britain (24, 40); these species do not normally harbor the indigenous 24.5-MDa plasmid, and attempts to introduce this plasmid into strains of *N. meningitidis* and other *Neisseria* spp. have generally been unsuccessful (17). However, it has been shown experimentally that the 25.2-MDa plasmids may be transferred by conjugation, maintained, and transferred back to *N. gonorrhoeae* from *N. meningitidis*, as well as to the other *Neisseria* spp. tested (35).

Both the 24.5- and the 25.2-MDa plasmids can mobilize the gonococcal 4.4- and 3.2-MDa β-lactamase plasmids to a variety of bacterial species. However, when the 24.5-MDa plasmid is used to mobilize the β-lactamase plasmids, only *N. gonorrhoeae* and some of the *N. cinerea* transconjugants receive or maintain the 24.5-MDa plasmid (17). When the 25.2-MDa plasmid was used to mobilize the β-lactamase plasmids, all transconjugants, with the exception of some *N. cinerea* recipients, acquired and maintained the 25.2-MDa plasmid, whereas fewer transconjugants acquired the β-lactamase plasmid (36). Thus, the 25.2-MDa plasmid differs from the ancestral 24.5-MDa plasmid by its wide natural host range, while retaining its ability to mobilize the β-lactamase plasmids between strains. It is not known whether the ability of the 25.2-MDa plasmid to transfer to many bacterial species is due to the direct influence of the TetM genes, or whether the TetM determinant was inserted into the 24.5-MDa plasmid in such a way that it has altered or deleted DNA sequences that previously restricted the ability of the 24.5-MDa plasmid to be accepted or maintained in other bacterial species.

RSF1010-Like Plasmids

Recently, a new group of plasmids ranging in size from 4.9 to 9.4 MDa has been described for *N. meningitidis*, *N. mucosa*, *N. subflava*, and *N. sicca* (14, 29, 38). These plasmids are genetically related to the enteric plasmid RSF1010 which is an IncQ(P-4) plasmid that encodes streptomycin and sulfonamide resistance owing to the production of a streptomycin phosphotransferase and sulfonamide-resistant dihydropteroate synthetase (14, 38). A related plasmid has also been found in *Eikenella corrodens* (37). Some of these plasmids specify resistance to sulfonamide alone, whereas others specify resistance to penicillin, streptomycin, and sulfonamide (14, 29, 37, 38). In some cases, the relationship of the *Neisseria* plasmids to the ancestral RSF1010 plasmid has been based on DNA homology with the RSF1010 plasmid, including the antibiotic resistance region as well as regions outside the antibiotic resistance genes (29, 37, 38). In other cases, the relationship between the *Neisseria* plasmids has been based on more circumstantial data, such as similarities between the proteins encoded by the antibiotic resistance genes (14).

Plasmids encoding streptomycin, sulfonamide, and TEM-type β-lactamase resistance have been isolated from *N. mucosa*, *N. subflava*, *N. sicca*, and *Eikenella corrodens* (29, 37, 38), whereas plasmids specifying resistance to sulfonamide alone have been found in *N. meningitidis* strains (14). All of the multiresistance plasmids can be transferred by transformation and maintained in *E. coli* (29, 37, 38). The *N. meningitidis* sulfonamide resistance plasmid has been transferred by transformation and maintained in *N. gonorrhoeae* (14). This sulfonamide resistance plasmid may have been created (by the deletion of the streptomycin gene) from RSF1010 and then introduced into *N. meningitidis*. However, the *N. meningitidis* plasmid is larger than the RSF1010 ancestral plasmid, suggesting that it may have been created by a deletion of the streptomycin gene from RSF1010 followed by the insertion of other sequences or by the duplication of existing sequences (14).

The data obtained by several investigators suggest that the multiresistance plasmids carrying streptomycin, sulfonamide, and TEM β-lactamase (14, 38) were created by the transposition of Tn*A* onto RSF1010. These plasmids were subsequently spread, by mobilization or transformation, to other bacterial strains. The fact that the transposition of Tn*3* onto RSF1010-related plasmids occurs under laboratory conditions would support this hypothesis (20). However, there are differences between the naturally occurring plasmids and those created in the laboratory. The laboratory-created plasmids carry the whole Tn*3* transposon, whereas the naturally occurring plasmids do not (20). The possession of an incomplete Tn*3*-like segment by the multiresistance plasmids found in commensal *Neisseria* species is the only similarity between them and the gonococcal β-lactamase plasmids.

Other Plasmids

Robledano et al. (L. Robledano, M. J. Rivera, P. Madero, M. A. Marco, I. Otal, M. C. Aqudo and R. Gomez-Lus, Abstr. 5th Int. Congr. Chemother. 1987) reported the presence of a 29-MDa plasmid coding for ampicillin, tetracycline, streptomycin, kanamycin, neomycin and lividomycin resistance in a strain of *N. sicca*. The plasmid coded for two aminoglycoside-modifying enzymes, APH(3″) and APH(3′). This plasmid was conjugally transferred to an *N. sicca* but not to an *E. coli* recipient strain, suggesting that it was not of enteric origin. The genetic relationship of this plasmid to other *Neisseria* plasmids has not been determined, and, as a result, the origin of this plasmid is unclear.

CONCLUSIONS

The 2.6- and 24.5-MDa plasmids have been found in isolates of *N. gonorrhoeae* preserved since the 1940s (34). In contrast, plasmids carrying antibiotic resistance genes are relatively new; the β-lactamase plasmids appeared in the 1970s (12) and the TetM-containing plasmids in the 1980s (25). Most of the antibiotic resistance genes that have spread into *Neisseria* spp. are associated with transposons. These determinants can either be introduced into new species on

plasmids capable of being maintained in the host, such as the broad-host-range enteric RSF1010-like plasmid or the *Haemophilus* β-lactamase plasmid, or be integrated into indigenous host plasmids as seen with the 25.2-MDa plasmid. In either case, once the R factor is created or introduced, it can then be spread by conjugation or mobilization to other strains, other species within the same genus, and other genera of bacteria. Transformation may play a role in plasmid spread between strains, because many of the plasmids discussed above have been experimentally transferred to various hosts by transformation (39). However, deletions often appear in these plasmids during transformation, and the frequency of transfer by transformation is usually significantly lower than the frequency of transfer by conjugation (39).

Gene spread has also occurred in the genus *Neisseria* as a result of the transfer of antibiotic resistance genes associated with the conjugative transposon, TetM (24). Clinical isolates of commensal *Neisseria* species have been isolated that have the TetM determinant integrated into their chromosome (24). The fact that commensal *Neisseria* spp. can acquire and maintain the 25.2-MDa plasmid if given the opportunity (35) suggests that the commensal *Neisseria* strains have not acquired the TetM determinant from *N. gonorrhoeae* but rather from other bacterial species. This would explain why in the laboratory the 25.2-MDa plasmid is stable in the commensal *Neisseria* spp. but all the natural clinical isolates carry the TetM determinant in the chromosome.

The RSF1010-like plasmids, in general, appear to be rather limited in their geographical distribution; this may be because very few investigators have examined commensal *Neisseria* spp. for antibiotic resistance genes. The recent observation that the RSF1010-like plasmids can carry not only the sulfonamide-resistant dihydropteroate synthetase and streptomycin phosphotransferase (normally associated with this plasmid) but also the TEM β-lactamase is of interest. The RSF1010-like plasmids are the first multiresistance plasmid group found in *Neisseria* spp. The versatility in the number of antibiotic resistance genes which the RSF1010-like plasmid can carry is unique among the neisserial plasmids. In addition, these plasmids are found in a number of different species. Since the RSF1010-like plasmid has already been found in *N. meningitidis*, it is very possible that this plasmid group will be disseminated to *N. gonorrhoeae*; therefore, more work to characterize this plasmid family should be done.

The number of plasmids carrying antibiotic resistance genes has increased in the genus *Neisseria* over the past 10 years. This increase is due not only to an increase in the number of strains carrying the previously described plasmids, but also to the identification of new plasmids carrying a number of different antibiotic resistance determinants in various commensal *Neisseria* spp. The antibiotic resistance genes currently found have all been identified in other bacterial genera, usually enteric species, and, with the exception of the TetM determinant, all plasmids carrying antibiotic resistance genes appear to have originated in other gram-negative bacteria. The TetM determinant appears to have originated in gram-positive streptococci (28). It might be anticipated that when the prevalence of plasmids and antibiotic resistance genes increases in other bacteria, especially the enteric species, it may lead to the transfer of these plasmids and antibiotic resistance genes to *Neisseria* spp. It is important, therefore, to continue screening isolates of both pathogenic and nonpathogenic *Neisseria* spp. for antibiotic resistance and then to determine whether the resistance is due to the acquisition of new genetic material or to chromosomal mutation. The commensal species have been shown to carry multiresistance plasmids and may act as reservoirs for plasmids and antibiotic resistance genes that might be transferred to the pathogenic *Neisseria* species at a later date. Antimicrobial therapy for gonorrhea and meningitis may be more complicated in the future if these multiresistance plasmids become established in the pathogenic *Neisseria* spp.

ACKNOWLEDGMENTS

This work was supported by Public Health Service grants AI24136 and DEO8049 from the National Institutes of Health.

LITERATURE CITED

1. **Aalen, R. B., and W. B. Gundersen.** 1985. Polypeptides encoded by cryptic plasmids from *Neisseria gonorrhoeae*. Plasmid **14:** 209–216.
2. **Aalen, R. B., and W. B. Gundersen.** 1987. Molecular characterization and comparison of plasmid content in seven different strains of *Neisseria gonorrhoeae*. Acta Pathol. Microbiol. Immunol. Scand. Sect. B. **95:**13–21.
3. **Botha, P.** 1988. Penicillin-resistant *Neisseria meningitidis* in southern Africa. Lancet **i:**54.
4. **Brunton, J., D. Clare, and M. Meier.** 1986. Molecular epidemiology of antibiotic resistance plasmids of *Haemophilus* species and *Neisseria gonorrhoeae*. Rev. Infect. Dis. **8:**713–724.
5. **Chen, S.-T., and R. C. Clowes.** 1987. Nucleotide sequence comparisons of plasmids pHD131, pJB1, pFA3, and pFA7 and β-lactamase expression in *Escherichia coli*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae*. J. Bacteriol. **169:**3124–3130.
6. **Dickgiesser, N.** 1984. A molecular characterization of *H. influenzae* plasmid pVe445: a comparison with *N. gonorrhoeae* plasmids pNG10 and pNG18. Plasmid **11:**99–101.
7. **Dickgiesser, N., P. M. Bennett, and M. N. Richmond.** 1982. Penicillinase-producing *Neisseria gonorrhoeae* a molecular comparison of 5.3- and 7.4-kilobase β-lactamase plasmids. J. Bacteriol. **151:**1171–1175.
8. **Dillon, J. R., and M. Pauze.** 1981. Relationship between plasmid content and auxotype in *Neisseria gonorrhoeae* isolates. Infect. Immun. **33:**625–628.
9. **Dillon, J. R., M. Pauze, and K.-H. Yeung.** 1983. Spread of penicillinase-producing and transfer plasmids from the gonococcus to *Neisseria meningitidis*. Lancet **i:**779–781.
10. **Eisenstein, B. I., T. Sox, G. Biswas, E. Blackman, and P. F. Sparling.** 1977. Conjugal transfer of the gonococcal penicillinase plasmid. Science **195:**998–1000.
11. **Elwell, L. P., and S. Falkow.** 1975. Plasmids of the genus *Neisseria*, p. 137–154. *In* R. B. Roberts (ed.), The gonococcus. John Wiley & Sons, Inc., New York.
12. **Elwell, L. P., M. Roberts, L. W. Mayer, and S. Falkow.** 1977. Plasmid-mediated beta-lactamase production in *Neisseria gonorrhoeae*. Antimicrob. Agents Chemother. **11:**528–533.
13. **Engelkirk, P. G., and D. E. Schoenhard.** 1972. Physical evidence of a plasmid in *Neisseria gonorrhoeae*. J. Infect. Dis. **127:** 197–200.
14. **Facinelli, B., and P. E. Varaldo.** 1987. Plasmid-mediated sulfonamide resistance in *Neisseria meningitidis*. Antimicrob. Agents Chemother. **31:**1642–1643.
15. **Fayet, O., Y. Fromert, and J. C. Piffaretti.** 1982. Beta-lactamase-specifying plasmids isolated from *Neisseria gonorrhoeae* have retained an intact right part of a Tn*3*-like transposon. J. Bacteriol. **149:**136–144.
16. **Flett, F., B. O. Humphreys, and J. R. Saunders.** 1981. Intraspecific and intergeneric mobilization of non-conjugative resistance plasmids by a 24.5 megadalton conjugative plasmid of *Neisseria gonorrhoeae*. J. Gen. Microbiol. **125:**123–129.
17. **Genco, C. A., J. S. Knapp, and V. L. Clark.** 1984. Conjugation of plasmids of *Neisseria gonorrhoeae* to other *Neisseria* species: potential reservoirs for the β-lactamase plasmid. J. Infect. Dis. **150:**397–401.

18. **Guiney, D. G., and J. I. Ito, Jr.** 1982. Transfer of the gonococcal penicillinase plasmid: mobilization in *Escherichia coli* by IncP plasmids and isolation as a DNA-protein relaxation complex. J. Bacteriol. **150**:298–302.
19. **Hagblom, P., C. Korch, A.-B. Jonsson, and S. Normark.** 1986. Intragenic variation by site-specific recommendation in the cryptic plasmid of *Neisseria gonorrhoeae*. J. Bacteriol. **167**: 231–237.
20. **Heffron, R., C. Rubens, and S. Falkow.** 1977. Transportation of a plasmid DNA sequence that mediates ampicillin resistance: identity of laboratory-constructed plasmids and clinical isolates. J. Bacteriol. **129**:530–533.
21. **Ikeda, F., A. Tsuji, Y. Kaneko, M. Nishida, and S. Goto.** 1986. Conjugal transfer of beta-lactamase-producing plasmids of *Neisseria gonorrhoeae* to *Neisseria meningitidis*. Microbiol. Immunol. **30**:737–742.
22. **Ison, C. A., C. M. Beillinger, and J. Walker.** 1986. Homology of cryptic plasmid of *Neisseria gonorrhoeae* with plasmids from *Neisseria meningitidis* and *Neisseria lactamica*. J. Clin. Pathol. **39**:1119–1123.
23. **Ison, C. A., P. Terry, K. Bindayna, M. J. Gill, J. Adams, and N. Woodford.** 1988. Tetracycline-resistant gonococci in UK. Lancet **i**:651–652.
24. **Knapp, J. S., S. R. Johnson, J. M. Zenilman, M. C. Roberts, and S. A. Morse.** 1988. High-level tetracycline resistance due to *tetM* in strains of *Neisseria* species, *Kingella denitrificans*, and *Eikenella corrodens*. Antimicrob. Agents Chemother. **32**:765–767.
25. **Knapp, J. S., J. M. Zenilman, J. W. Biddle, G. H. Perkins, W. E. DeWitt, M. L. Thomas, S. R. Johnson, and S. A. Morse.** 1987. Frequency and distribution in the United States of strains of *Neisseria gonorrhoeae* with plasmid-mediated, high-level resistance to tetracycline. J. Infect. Dis. **155**:819–822.
26. **Korch, C., P. Hagblom, H. Ohman, M. Goransson, and S. Normark.** 1985. Cryptic plasmid of *Neisseria gonorrhoeae*: complete nucleotide sequence and genetic organization. J. Bacteriol. **163**:430–438.
27. **McNicol, P. J., W. L. Albritton, and A. R. Ronald.** 1986. Transfer of plasmid-mediated ampicillin resistance from *Haemophilus* and *Neisseria gonorrhoeae* requires an intervening organism. Sex. Transm. Dis. **13**:145–150.
28. **Morse, S. A., S. R. Johnson, J. W. Biddle, and M. C. Roberts.** 1986. High-level tetracycline resistance in *Neisseria gonorrhoeae* is the result of acquisition of streptococcal *tetM* determinant. Antimicrob. Agents Chemother. **30**:664–670.
29. **Pintado, C., C. Salvador, R. Rotger, and C. Nombela.** 1985. Multiresistance plasmid from commensal *Neisseria* species. Antimicrob. Agents Chemother. **27**:120–124.
30. **Prere, M. R., O. Fayet, C. Delmas, M. B. Lareng, and H. Dabernat.** 1985. Presence de plasmides chez *Neisseria meningitidis*. Ann. Inst. Pasteur Microbiol. **136A**:271–276.
31. **Roberts, M., L. P. Elwell, and S. Falkow.** 1977. Molecular characterization of two beta-lactamase-specifying plasmids isolated from *Neisseria gonorrhoeae*. J. Bacteriol. **131**:557–563.
32. **Roberts, M., and S. Falkow.** 1977. Conjugal transfer of R plasmids in *Neisseria gonorrhoeae*. Nature (London) **266**:630–631.
33. **Roberts, M., and S. Falkow.** 1979. In vivo conjugal transfer of R plasmids in *Neisseria gonorrhoeae*. Infect. Immun. **24**:982–984.
34. **Roberts, M., P. Piot, and S. Falkow.** 1979. The ecology of gonococcal plasmids. J. Gen. Microbiol. **114**:491–494.
35. **Roberts, M. C., and J. S. Knapp.** 1988. Host range of the conjugative 25.2-megadalton tetracycline resistance plasmid from *Neisseria gonorrhoeae*. Antimicrob. Agents Chemother. **32**:488–491.
36. **Roberts, M. C., and J. S. Knapp.** 1988. Transfer of β-lactamase plasmids from *Neisseria gonorrhoeae* to *Neisseria meningitidis* and commensal *Neisseria* species by the 25.2-megadalton plasmid. Antimicrob. Agents Chemother. **32**:1430–1432.
37. **Rotger, R., E. Garcia-Valdes, and E. P. Trallero.** 1986. Characterization of a β-lactamase-specifying plasmid isolated from *Eikenella corrodens* and its relationship to a commensal *Neisseria* plasmid. Antimicrob. Agents Chemother. **30**:508–509.
38. **Rotger, R., F. Rubio, and C. Nombela.** 1986. A multi-resistance plasmid isolated from commensal *Neisseria* species is closely related to the enterobacterial plasmid RSF1010. J. Gen. Microbiol. **132**:2491–2496.
39. **Sox, T. E., W. Mohammed, and P. F. Sparling.** 1979. Transformation-derived *Neisseria gonorrhoeae* plasmids with altered structure and function. J. Bacteriol. **138**:510–518.
40. **Sprott, M. S., A. M. Kearns, and J. M. Field.** 1988. Penicillin-insensitive *Neisseria meningitidis*. Lancet **i**:1167.
41. **van Embden, J. D. A., M. Dessens, and B. van Klingeren.** 1985. A new β-lactamase plasmid in *Neisseria gonorrhoeae*. J. Antimicrob. Chemother. **15**:247–258.
42. **Verschueren, H., M. Dekegel, D. Dekegel, C. Gilquin, and S. De Mayer.** 1982. Plasmids in *Neisseria meningitidis*. Lancet **i**: 851–852.
43. **Yeung, K.-H., J. R. Dillon, M. Pauze, and E. Wallace.** 1986. A novel 4.9-kilobase plasmid associated with an outbreak of penicillinase-producing *Neisseria gonorrhoeae*. J. Infect. Dis. **153**:1162–1165.